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(54) Titre : SYSTEME D'ESSAI PERMETTANT D'EVALUER LA COMPATIBILITE DE SUBSTANCES BIOLOGIQUEMENT
ACTIVES AVEC DES COPOLYMERES

(54) Title: TEST SYSTEM FOR EVALUATING THE COMPATIBILITY OF BIOLOGICALLY ACTIVE SUBSTANCES WITH
COPOLYMERS

(57) Abrégé/Abstract:

A test solution agent, a test system and a method for evaluating the compatibility of biologically active substances with N-vinylpyrrolidone copolymers are disclosed.



Abstract

A test solution agent, a test system and a method for evaluating the compatibility of biologically active substances with N-vinylpyrrolidone copolymers are disclosed.

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Test system for evaluating the compatibility of
biologically active substances with copolymers

The present invention relates to a liquid mixture
5 serving as test solvent, and to a test system and a
method for evaluating the compatibility of biologically
active substances with N-vinylpyrrolidone copolymers
using the liquid mixture.

10 Solid dispersions, i.e. homogeneous microdisperse
phases of two or more solids and the special case of
so-called solid solutions (molecular dispersion
systems), and their use in pharmaceutical technology
are generally known, cf. Chiou and Riegelman J. Pharm.
15 Sci., 60, 1281 - 1300 (1997).

Solid solutions can be produced by melting processes or
by the solution process. Particularly suitable as
polymeric excipient for producing such solid
20 dispersions or solid solutions are N-vinylpyrrolidone
copolymers, i.e. copolymers of N-vinylpyrrolidone with
further ethylenically unsaturated monomers. Solid
solutions of biologically active substances based on
such copolymers can be produced particularly
25 advantageously by melt extrusion as described, for
example, in EP-A 240 904.

However, there are minimum requirements on the amounts
employed to produce melt extrudates. If only relatively
30 small amounts of active ingredient are available, it
cannot be predicted with certainty whether an active
ingredient will form a solid solution together with the
chosen copolymer. However, it is precisely when drug
products based on new active ingredients are being
35 developed that only relatively small amounts of the
active ingredient are frequently available, so that the
possibility of prediction with the aid of a simple test
system appears to be extremely desirable.

It is likewise desirable to be able to make predictions concerning the stability of solid solutions or solid dispersions. This is because, depending on the compatibility of the active ingredient with the copolymer, the previously homogeneous disperse phase may become inhomogeneous, or the active ingredient may recrystallize. Such phase separation or recrystallization is unwanted because of the change in the homogeneity and the release characteristics associated therewith.

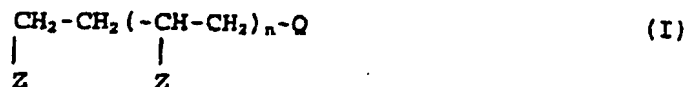
EP-A 0987549 discloses a test system for characterizing the compatibility of biologically active substances with polyvinylpyrrolidone in a solid dispersion.

It is the object of the present invention to indicate a test system with the aid of which it is possible to predict the compatibility of biologically active substances and N-vinylpyrrolidone copolymers in a simple manner.

It has surprisingly been found that the dissolving properties of N-vinylpyrrolidone copolymers can be simulated by a liquid mixture of 1,3-bis(pyrrolidon-1-yl)butane with certain compounds which have structural similarity to the comonomer units present in the copolymer.

The invention therefore relates to a liquid mixture which comprises

- a) 1,3-bis(pyrrolidon-1-yl)butane and
- b) at least one compound of the formula I



35

in which

Q is $\text{CH}_2\text{-Z}$, $\text{CH}_2\text{-CH}_2\text{-Z}$ or $\text{CH}_2\text{-C}_1\text{-C}_4\text{-alkyl}$,

n is 0, 1, 2 or 3, and
the Z radicals are C₁-C₂₀-alkylcarbonyloxy, carboxyl,
C₁-C₂₀-alkyloxycarbonyl, C₂-C₄-hydroxyalkyloxycarbonyl,
di(C₁-C₄-alkyl)amino-C₂-C₄-alkyloxycarbonyl or tri(C₁-C₄-
5 alkyl)ammonium-C₂-C₄-alkyloxycarbonyl.

All the Z radicals occurring in formula I are preferably identical. "Liquid mixture" is intended for the purposes of the present application to mean that
10 the mixture is in liquid form at least at slightly elevated temperature, e.g. at 45°C, preferably even at room temperature.

The liquid mixture serves as test solvent which
15 simulates the dissolving properties of the N-vinylpyrrolidone copolymer. The liquid mixture normally contains components a) and b) in a ratio of from 10:1 to 1:10, preferably 5:1 to 1:5, by weight.

20 The invention additionally relates to a test system for evaluating the compatibility of a biologically active substance with a copolymer which includes units of N-vinylpyrrolidone and of at least one ethylenic unsaturated monomer of the formula II

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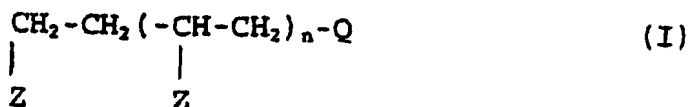
in which R is hydrogen or methyl, and Z' has the meaning indicated above for Z, where the test system
30 includes the liquid mixture defined above and at least one biologically active substance.

The invention additionally relates to a method for evaluating the compatibility of a biologically active
35 substance with an N-vinylpyrrolidone copolymer, where the copolymer includes units of N-vinylpyrrolidone in a proportion by weight of x_{VP} and units of at least one ethylenically unsaturated monomer of the formula II



in which R is hydrogen or methyl, Z' is C₁-C₂₀-alkyl-carbonyloxy, carboxyl, C₁-C₂₀-alkyloxycarbonyl, C₂-C₄-hydroxyalkyloxycarbonyl, di(C₁-C₄-alkyl)amino-C₂-C₄-alkyloxycarbonyl or tri(C₁-C₄-alkyl)ammonium-C₂-C₄-alkyloxycarbonyl, in a proportion by weight of x_M, in which

- 10 a) a test solvent which comprises 1,3-bis(pyrrolidone-1-yl)butane in a proportion by weight of x_{VP} and a compound of the formula I in a proportion by weight of x_M



15

in which Q is CH₂-Z, CH₂-CH₂-Z or CH₂-C₁-C₄-alkyl, n is 0, 1, 2 or 3, the Z radicals are identical and correspond to the Z' radical, is prepared,

- 20 b) the biologically active substance is brought into contact with the test solvent, and
c) the phase behavior of the mixture and/or solubility of the biologically active substance in the test solvent is determined.

25

X_{VP} is in general from 10 to 90% by weight, usually 30 to 70% by weight. x_M is in general from 90 to 10% by weight, usually 70 to 30% by weight. If more than one monomer of the formula II is present, the individual contribution of the various monomers x_{M1}, x_{M2}, ... are to be put for x_M.

30

The radicals Z and Z' are preferably C₁-C₄-alkyl-carbonyloxy, carboxyl, C₁-C₄-alkyloxycarbonyl or C₂-C₄-hydroxyalkyloxycarbonyl. If Z or Z' are tri(C₁-C₄-alkyl)ammonium-C₂-C₄-alkyloxycarbonyl, they are accompanied by one equivalent of a pharmaceutically

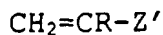
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acceptable anion such as hydroxide, sulfate, hydrogen-sulfate, carbonate, hydrogencarbonate, a halide, in particular chloride, the anion of an organic acid such as acetate, lactate, fumarate, or the like. If Z or Z' are carboxyl, the carboxyl group may also be wholly or partly neutralized, in which case suitable charge-balancing cations are pharmaceutically acceptable cations such as alkali metal or alkaline earth metal ions, e.g. sodium or potassium, or unsubstituted or substituted ammonium ions such as dimethylammonium, trimethylammonium, diethanolammonium and the like.

1,3-Bis(pyrrolidon-1-yl)butane can be obtained by dimerization of N-vinylpyrrolidone under acidic reaction conditions and subsequent hydrogenation of the resulting 1,3-bis(pyrrolidon-1-yl)butene to 1,3-bis(pyrrolidon-1-yl)butane (cf. Breitenbach et al., Naturwissenschaften 42, 955, 155; 440). 1,3-Bis(pyrrolidon-1-yl)butane is a colorless oily liquid with a boiling point of 205 to 215°C (0.2 mbar).

The compounds of the general formula I are either commercially available or can be prepared in a simple manner. Use for example of 1,3-diacetoxybutane and, in particular, 1,4-diacetoxybutane as compound of the formula I has been successful. Compounds of the formula I can be obtained for example by esterification of polyols such as 1,3-butanediol, 1,4-butanediol or 1,3,5-pentanetriol with carboxylic acids such as acetic acid or derivatives thereof or by esterification of polycarboxylic acids such as glutaric acid or adipic acid with suitable alcohols.

Suitable copolymers whose compatibility with biologically active substances can be evaluated with the aid of the test system of the invention are copolymers of N-vinylpyrrolidone with ethylenically unsaturated monomers of the formula II



(II)

in which R is hydrogen or methyl, and Z' is C₁-C₂₀-alkylcarbonyloxy, carboxyl, C₁-C₂₀-alkyloxycarbonyl, C₂-C₄-hydroxyalkyloxycarbonyl, di(C₁-C₄-alkyl)amino-C₂-C₄-alkyloxycarbonyl or tri(C₁-C₄-alkyl)ammonium-C₂-C₄-alkyloxycarbonyl.

Monomers of the formula II which may be mentioned are vinyl esters of C₁-C₂₀-alkanecarboxylic acids, such as vinyl acetate or vinyl propionate, acrylic or methacrylic acid; C₁-C₂₀-alkyl esters of acrylic acid or methacrylic acid, such as methyl acrylate, methyl methacrylate, ethyl acrylate, ethyl methacrylate, C₂-C₄-hydroxyalkyl (meth)acrylates such as hydroxyethyl acrylate, di(C₁-C₄-alkyl)amino-C₂-C₄-alkyl (meth)acrylates such as dimethylaminopropyl acrylate, or (meth)acryloyloxy-C₂-C₄-alkyltri(C₁-C₄-alkyl)ammonium salts such as acryloyloxypropyltrimethylammonium chloride.

The preferred copolymers include those of N-vinylpyrrolidone and vinyl acetate, especially in a ratio of 70:30 to 30:70 by weight; and copolymers of N-vinylpyrrolidone with methyl methacrylate, especially in a ratio of from 20:80 to 55:45 by weight.

The copolymers generally have a Fikentscher K value of from 10 to 110, in particular from 20 to 80.

The radical Z in the compound of the formula I is chosen in accordance with the radical Z' in the comonomer of the copolymer to be simulated. Thus, for example, a mixture of 1,3-bis(pyrrolidon-1-yl)butane with 1,4-diacetoxybutane serves to simulate the dissolving properties of N-vinylpyrrolidone/vinyl acetate copolymers. It is, of course, possible for the copolymer to be simulated also to contain two or more different monomers of the formula II. The test solvent

is then prepared by using two or more different compounds of the formula I with appropriately chosen radicals Z as component b).

5 Compatibility means for the purposes of the present application the ability of a substance to form with the N-vinylpyrrolidone copolymer a homogeneous, stable solid dispersion, this solid dispersion being in particular a solid solution, i.e. a molecular
10 dispersion of the components in one another. The test system is suitable in principle for all active pharmaceutical ingredients, crop protection agents, food supplements or cosmetic active ingredients. It is also possible to investigate detergents or dyes for
15 their compatibility with the copolymers. The influence of formulation aids which are not themselves biologically active, such as sugars, sugar alcohols, solubilizers such as surfactants, or other polymeric aids, can also be investigated.

20 The method of the invention is carried out by first preparing a test solvent. The test solvent comprises 1,3-bis(pyrrolidon-1-yl)butane and a compound of the formula I in a ratio by weight which corresponds to
25 that of N-vinylpyrrolidone and comonomer(s) in the copolymer to be simulated. The solubility of the biologically active substance to be investigated in the liquid mixture is then assessed at a defined temperature, usually room temperature. The solubility
30 can be determined quantitatively, e.g. in % by weight based on the weight of test solvent and biologically active substance. In many cases, it is sufficient to state whether the solubility is greater or less than a particular value. For this purpose, a predetermined
35 amount of the biologically active substance is brought into contact with the test solvent. The quantitative ratios can in principle be chosen freely. However, it is advisable to choose the concentration ranges in the test system such that they correspond to the active

ingredient content typical of extrudate forms, i.e. generally from 0.1 to 70% by weight, preferably 10 to 30% by weight, of biologically active substance, based on the total weight of the test system.

5

The biologically active substance is normally weighed out, mixed with the test solvent and preferably blended, e.g. stirred with a laboratory magnetic stirrer at from 5 to 2000 rpm, or treated with
10 ultrasound or a vortex homogenizer. Dissolving can also be speeded up by heating the test system. The heating preferably takes place in such a way that the heating rate approximately corresponds to that in a melt formulation, i.e. at from 0.5 to 5°C/min. The test
15 system is preferably heated to a maximum of 140°C, e.g. to a temperature in the range from 45 to 140°C or 110 to 140°C. However, heating to the boiling point of the liquid mixture is also possible in the individual case. The test system is then allowed to cool to the
20 determination temperature, usually room temperature.

The phase behavior of the mixture is then assessed, i.e. it is established by visual, spectroscopic and/or thermoanalytical investigation of the resulting mixture
25 whether the biologically active substance is able to form a homogeneous phase with the liquid mixture.

Visual inspection takes place for example using a microscope such as a usual optical microscope. It is
30 established in this case whether a clear solution has formed. Besides visual inspection, also suitable is a spectroscopic investigation of the test system. For example, the test system can be investigated for its amorphous character with the aid of confocal Raman
35 spectroscopy. Also suitable is the method of differential scanning calorimetry. It is possible to conclude from the presence of a homogeneous phase that the solubility of the biologically active substance is greater than the concentration of the substance in the

dissolving test. Conversely, a lower solubility can be concluded from the occurrence of a phase separation.

Quantitative determination of the solubility is possible for example in the following way:

5 a) A concentration series is prepared by bringing various amounts of biologically active substance into contact with a constant amount of test solvent in parallel tests. After an equilibration time over a
10 defined period at a given temperature, preferably with blending, e.g. stirring for 24 hours or ultrasound treatment for 30 min, the maximum concentration at which clear solutions are obtained is found. The solubility of the biologically active substance is
15 between the concentration at which a clear solution is obtained but at the next concentration no clear solution is obtained.

b) An amount of the test solvent which is
20 insufficient for completely dissolving is added to an amount of the biologically active substance, or further amounts of biologically active substance are added to the solution until the added amount no longer completely dissolves. After an equilibration time over
25 a defined period at a given temperature, preferably with blending, e.g. stirring for 24 hours or ultrasound treatment for 30 min, a sample of the clear supernatant is taken. The mixture can for this purpose be previously centrifuged, e.g. using an ultracentrifuge
30 at 8000 to 12 000 rpm. The concentration of the biologically active substance is determined in the sample of the clear supernatant, e.g. by high pressure liquid chromatography (HPLC). The value which is found corresponds to the solubility of the biologically
35 active substance.

It is possible by means of the methods mentioned above to determine, depending on the equilibration conditions, the thermodynamic saturation solubility or

the maximum (kinetic) solubility.

The solubility found after 24 hours at room temperature ($22^{\circ}\text{C} \pm 2^{\circ}\text{C}$) essentially corresponds to the thermodynamic saturation solubility of the biologically active substance. This value of the solubility is a measure of the thermodynamic saturation solubility of the biologically active substance in the matrix of the copolymer at room temperature. Solid solutions of biologically active substances are thermodynamically stable if the active ingredient loading is below the thermodynamic saturation solubility of the biologically active substance in the matrix.

However, the active ingredient loading in solid solutions can be increased greatly by energy input. The maximum active ingredient loading achievable in a given matrix of a copolymer can be predicted with the test system of the invention by determining the solubility of the biologically active substance in accordance with one of the aforementioned methods a) or b), the equilibration being carried out by heating to a temperature of, for example, 140°C , in particular from 110 to 140°C , or by sonication.

The test system of the invention also allows the recrystallization behavior to be predicted. Especially for test systems in which higher active ingredient loadings than the thermodynamic saturation solubility have been set up by energy input, e.g. heating or sonication, the recrystallization behavior after the energy input ceases or after cooling to room temperature represents an important criterion. Test systems in which the biologically active substance does not recrystallize immediately are investigated for long-term stability. It is possible to use the following conditions for this, for example:

- leaving to stand at room temperature for 24 hours,
- storage for one month, 3 months, 6 months in

climate zone 2 (25°C, 60% relative humidity) or
climate zone 4 (20°C, 70% relative humidity), or
- stress storage at 40°C, 75% relative humidity for
up to 6 months.

5

It is also possible with the aid of the test system of
the invention to investigate the influence of
excipients or a solubility-increasing or solubility-
reducing effect of the presence of a second or further
10 biologically active substance on the solubility of a
first biologically active substance in the matrix of
the copolymer. For this purpose, these excipients, e.g.
solubilizers, or further biologically active substances
are added to the test solvent in addition to the
15 biologically active substance to be tested. It is then
possible again to determine the thermodynamic
saturation solubility and/or the maximum solubility as
indicated above.

20 The invention is illustrated in more detail by the
following examples.

Example 1: Thermodynamic saturation solubility of
lopinavir in a matrix of a copolymer of N-vinyl-
25 pyrrolidone and vinyl acetate (60:40).

The copolymer was simulated by a mixture of 1,3-bis-
(pyrrolidon-1-yl)butane and 1,4-diacetoxybutane in the
ratio of 6:4 by weight.

30

Method a)

In parallel tests, the active ingredient was weighed
into glass bottles and made up with the test solvent
appropriate for the concentrations indicated in the
35 table below (all concentrations in weight/weight). All
seven samples were provided with a magnetic stirring
bar and stirred at room temperature for 24 hours. It
was established by visual inspection that the active
ingredient formed clear solutions up to 24.1%; the test

with 26.0% showed incomplete dissolving. The saturation solubility was therefore between 24.1 and 26.0% by weight.

Lopinavir [%]	20.2	21.9	24.1	26.0	29.5	33.9	36.3
Clear solution	+	+	+	-	-	-	-

5

Method b)

In an alternative determination method, 150 mg of lopinavir were mixed with 350 mg of the test solvent and stirred at room temperature for 24 hours. The sample was then centrifuged at 12 000 rpm for one minute. The clear supernatant was investigated by HPLC. A solubility of 24.9% by weight was found.

Method c)

15 The maximum solubility was determined by mixing 60 mg of lopinavir with 140 mg of the test solvent and treating with ultrasound at room temperature for 30 min. The solvent was then centrifuged at 10 000 rpm for 10 min. A sample of the clear supernatant was
20 investigated by HPLC. A maximum solubility of 39.72% by weight was found. The remaining amount of the sample was stored at room temperature for 4 weeks. Then a further sample of the supernatant was taken and investigated by HPLC. A concentration of 28.87% by
25 weight was found.

Example 2: Thermodynamic saturation solubility of lopinavir under the influence of polyoxyethylene-glycerol trihydroxystearate (Cremophor RH 40®)

30

Example 1a) was repeated but with use of the concentrations indicated in the table below, and with the test solvent containing 5% by weight Cremophor RH 40. The saturation solubility was found to be
35 between 22.0 and 26.0%.

Lopinavir [%]	20.0	22.0	23.7	26.0	30.0	33.0	35.8
Cremophor [%]*	5	5	5	5	5	5	5
Clear solution	+	+	+	-	-	-	-

* based on the test solvent

Example 1b) was repeated but with the test solvent containing 5% by weight Cremophor RH 40. A solubility of 22.8% was found.

It was possible to show with the aid of the test system of the invention that Cremophor RH 40 reduces the thermodynamic saturation solubility of lopinavir.

Example 3: Thermodynamic saturation solubility of lopinavir under the influence of ritonavir

An active ingredient premix of the two abovementioned active ingredients in a ratio of 4:1 by weight was prepared. Example 1a) was repeated with this active ingredient mixture, the concentration being as in the table below.

Lopinavir [%]	19.2	20.6	23.9	27.8
Ritonavir [%]	4.8	5.2	6	6.9
Total active ingredient [%]	24.0	25.8	29.9	34.7
Clear solution	+	+	-	-

Example 1b) was repeated with the abovementioned active ingredient premix. 21.3% by weight lopinavir was found in the clear supernatant by HPLC. It was possible with the aid of the test system of the invention to show that the presence of ritonavir reduces the thermodynamic saturation solubility of lopinavir.

Example 4: Thermodynamic saturation solubility of lopinavir under the influence of ritonavir and Cremophor RH 40

- 5 Example 3a) was repeated, using the concentrations indicated in the table below, and with the test solvent containing 10% by weight Cremophor RH 40. Visual determination of the concentration series led to a thermodynamic saturation solubility for the active
10 ingredient mixture of between 23.6% and 28.0%. The HPLC method led to a result of 21.7% for lopinavir.

Lopinavir [%]	14.2	15.8	18.9	22.4
Ritonavir [%]	3.6	4.0	4.7	5.6
Total active ingredient [%]	17.8	19.8	23.6	28.0
Cremophor [%]*	10	10	10	10
Clear solution	+	+	+	-

* based on the test solvent

15 Example 5: Melt extrusion

- A formulation containing 18.7 parts by weight of lopinavir, 4.7 parts by weight of ritonavir, 10.0 parts by weight of Cremophor RH 40 and 100 parts by weight of
20 N-vinylpyrrolidone/vinyl acetate copolymer (60:40) was prepared for the melt extrusion. Melt extrusion of this formulation using a heated twin screw extruder resulted in stable solid solutions. After storage of the extrudates at room temperature for 8 months they
25 underwent X-ray investigation. Both active ingredients were in X-ray amorphous form, i.e. no recrystallization of an active ingredient took place. In accordance with the prediction of the test system, a stable solid solution of the active ingredients is present.

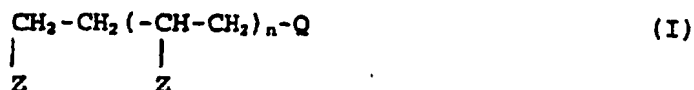
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Claims

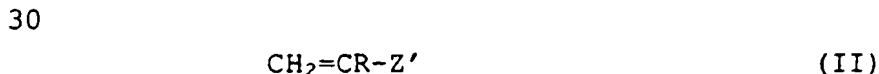
1. A liquid mixture comprising
- a) 1,3-bis(pyrrolidon-1-yl)butane and
- 5 b) at least one compound of the formula I



in which

- 10 Q is CH_2-Z , $\text{CH}_2-\text{CH}_2-\text{Z}$ or $\text{CH}_2-\text{C}_1-\text{C}_4-\text{alkyl}$,
 n is 0, 1, 2 or 3, and
 the Z radicals are C_1-C_{20} -alkylcarbonyloxy,
 carboxyl, C_1-C_{20} -alkyloxycarbonyl, C_2-C_4 -hydroxy-
 alkyloxycarbonyl, di(C_1-C_4 -alkyl)amino- C_2-C_4 -alkyl-
 15 oxy carbonyl or tri(C_1-C_4 -alkyl)ammonium- C_2-C_4 -
 alkyloxycarbonyl.

2. The mixture as claimed in claim 1, where component
- 20 b) is 1,4-diacetoxybutane.
3. The mixture as claimed in claim 1 or 2, in which
 components a) and b) are present in a ratio of
 from 10:1 to 1:10 by weight.
- 25 4. A test system for evaluating the compatibility of
 a biologically active substance with a copolymer
 which includes units of N-vinyl-pyrrolidone and
 of at least one ethylenic unsaturated monomer of
 the formula II



- 30 in which R is hydrogen or methyl, and Z' has the
 meaning indicated in claim 1 for Z, where the test
 35 system includes a liquid mixture as claimed in any
 of claims 1 to 3 and at least one biologically

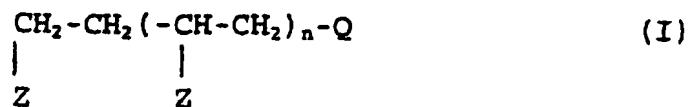
active substance.

5. The test system as claimed in claim 4, comprising from 10 to 70% by weight of biologically active substance.
6. The test system as claimed in claim 4 or 5, additionally comprising at least one formulation aid.
7. A method for evaluating the compatibility of a biologically active substance with an N-vinylpyrrolidone copolymer which includes units of N-vinylpyrrolidone in a proportion by weight of x_{VP} and units of at least one ethylenically unsaturated monomer of the formula II



- in which R is hydrogen or methyl, Z' is C₁-C₂₀-alkylcarbonyloxy, carboxyl, C₁-C₂₀-alkyloxy-carbonyl, C₂-C₄-hydroxyalkyloxy-carbonyl, di(C₁-C₄-alkyl)amino-C₂-C₄-alkyloxy-carbonyl or tri(C₁-C₄-alkyl)ammonium-C₂-C₄-alkyloxy-carbonyl, in a proportion by weight of x_M , in which

- a) a test solvent which comprises 1,3-bis-(pyrrolidon-1-yl)butane in a proportion by weight of x_{VP} and a compound of the formula I in a proportion by weight of x_M



- in which Q is CH₂-Z, CH₂-CH₂-Z or CHZ-C₁-C₄-alkyl, n is 0, 1, 2 or 3, the Z radicals are identical and correspond to the Z' radical, is prepared,
- b) the biologically active substance is brought

into contact with the test solvent, and

c) the phase behavior of the mixture and/or solubility of the biologically active substance in the test solvent is determined.

5

8. The method as claimed in claim 7, in which the phase behavior of the mixture is investigated visually, spectroscopically and/or thermo-analytically.

10

9. The method as claimed in claim 7 or 8, in which the mixture of biologically active substance and test solvent is heated to a temperature of up to 140°C.